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Is regular systemic opioid analgesia associated with shorter survival in adult patients with cancer? A systematic literature review.

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Abstract

Opioids are important in the management of pain in patients with cancer. Clinicians and patients are sometimes concerned about the effect of opioids on survival, which might decrease opioid prescription, compliance and symptom control. We wanted to determine whether opioid analgesia was associated with shorter survival in adult patients with cancer. We systematically searched for studies that assessed the effect of regular systemic opioid analgesia on survival. We identified 526 unique records, with 20 articles meeting inclusion criteria. Thirteen end-of-life studies, including 11 very low quality retrospective studies, did not find a consistent association between opioid analgesic treatment and survival, this evidence comes from low quality studies, so should be interpreted with caution. Seven longer-term studies, including 3 randomised controlled trials and 2 prospective studies were included. Six of these studies indicated that opioids were likely to be associated with a shorter survival. None of these studies were powered to assess the effect of opioids on survival as a primary endpoint. In view of this, no definitive conclusions can be made as to whether opioids affect survival in cancer patients. These data suggest that while opioid analgesia does not affect survival at the end of life, in the context of longer-term treatment, higher quality studies, with survival as a primary endpoint, are needed to confirm an independent association between opioid analgesia and shorter survival. An important limitation of research in this field is that the relationship between greater analgesic requirements and shorter survival may be mediated by painful progressive cancer.

Key words: opioid, morphine, pain, cancer, survival, prognosis

INTRODUCTION

Opioids are commonly used for pain management in patients with cancer [1,2]. There are international guidelines based on systematic review data for the use of opioids for cancer pain [3], however over 30% of patients remain undertreated [4]. As well as having beneficial effects, opioids have a range of adverse effects. These include constipation, emesis, cognitive dysfunction and addiction, as well as more recent concerns about effects on immune function, cancer growth and even their impact on survival [5-9]. Unwanted drug effects are a major concern for clinicians, patients and carers and affect opioid prescription and compliance which limit their use and potentially increase suffering caused by pain [4,7-14].

Opioids could potentially affect survival by having acute or chronic effects. Although there are differences between opioids, acute effects are primarily on respiratory drive (this is unlikely a major issue in appropriately used long term opioids in patients with cancer) or on the cardiac QTc interval causing torsades de pointes [15,16]. Opioids could potentially be associated with a longer survival due to improvements in pain, as higher pain scores in patients with cancer are associated with a shorter survival [17-20]. The chronic effects of opioids on survival could include effects on cancer growth which might be mediated by direct effects of opioids on host cells (including angiogenesis or actions on immune cells) or cancer cells (including cancer cell development, apoptosis and metastasis) [21-25], Figure 1. Opioids can inhibit components of both innate and adaptive immunity [21,22,26,27], although a recent systematic review of non-surgical patients with cancer did not find any studies which correlated immune function to clinical outcomes (e.g. cancer progression, recurrence and survival) [28]. In patients with advanced cancer, the systemic inflammatory response and cachexia decrease survival; opioids, via immune and endocrine effects, might influence cancer progression/recurrence and survival, although the overall effect of morphine on these outcomes in clinical practice is poorly understood [28-31].

These effects have been explored in preclinical models using morphine as the archetypical opioid, although there are differences between opioids [15,27]. The effect of intraoperative opioids in patients undergoing cancer surgery has been reviewed elsewhere [32-35]. Several long term retrospective studies have shown a benefit of the opioid-sparing effect of regional or spinal analgesia, alongside general anaesthesia, on cancer recurrence or survival in the resection of breast, prostate and colon tumours [36-38]. However other retrospective studies have not shown these benefits in prostate, colorectal, and cervical cancers even though there was a reduced need for postoperative opioids [39-41]. In surgery for early lung cancer, intraoperative opioids were associated with shorter survival, which was not the case in later stage disease [42]. A prospective multicentre randomised trial in abdominal cancer resection showed no effect of postoperative systemic opioids in cancer recurrence and mortality [43]. Previous reviews of opioids on survival have only included patients with advanced cancer and a short prognosis [44,45]. How regular systemic opioid analgesia impacts on survival in non-surgical patients with cancer is currently unknown [28], therefore this remains an important research question.

METHODS

Search strategy

We wanted to determine whether regular systemic opioid analgesia in adult patients with cancer was associated with shorter survival compared to adult patients with cancer not treated with regular systemic opioid therapy or treated with a lower dose of systemic opioids. We aimed to include previous reviews on opioids at the end of life, and expand upon them by including studies which examined the association between regular systemic opioid analgesia and survival in patients not at the end of life. This systematic review followed an a priori protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [46]. The review

protocol was registered on the PROSPERO website (<http://www.crd.york.ac.uk/PROSPERO>) before screening and data extraction (registration no. CRD42014013261) [47].

In August 2014 we searched the electronic databases Embase Classic+Embase (Ovid) 1947+; Ovid MEDLINE(R) 1946+; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; Conference Proceedings Citation Index -Science 1990+ (Web Of Science, Thomson Reuters); ClinicalTrials.gov (U.S. NIH); International Clinical Trials Registry Platform (WHO); CINAHL 1981+ (EbscoHost); Cochrane Database of Systematic Reviews (Wiley): Issue 7 of 12, 2014; Database of Abstracts of Reviews of Effect (Wiley): Issue 2 of 4, 2014; Cochrane Central Register of Controlled Trials (Wiley): Issue 6 of 12, 2014; and NHS Economic Evaluation Database (Wiley): Issue 2 of 4, 2014. Search strategies were devised to be inclusive of all potentially relevant studies using both Medical Subject Heading (MeSH) terms and text word searches to increase the search sensitivity. Terms for 'opioids', 'cancer' and 'survival' were combined to identify relevant studies. The search terms for opioids included individual drug names and generic terms 'opioids' and 'opiate'. The cancer search included the MeSH term 'exp neoplasms/' and text word searches for synonyms for cancer. The 'survival' search included terms and synonyms for life expectancy, mortality and time to death. Search strategies from all databases are available on request from the authors.

In addition to the electronic search, reference lists from identified publications were manually searched, as were previous reviews on opioids and survival and searches of the authors' own files. Experts in the field were consulted to ensure that no articles were missed. Unpublished studies were also included in the search. When only a conference abstract was available and the full study was unpublished, authors were contacted to try to ascertain further information. Searches were not restricted to English.

Inclusion, exclusion and selection criteria

Inclusion criteria: assessed the effect of opioids on survival of adult, human, patients with cancer (or predominantly cancer patients). Study types: randomised controlled trials, cohort studies, prospective and retrospective observational studies, database analysis.

Exclusion criteria: surgery (e.g. opioids for perioperative pain), opioids taken recreationally, opioids used for addiction. Study types: case studies.

Studies conducted in patients undergoing cancer surgery, healthy volunteers or animals were excluded from this systematic review as these groups have different opioid usage (duration, administration schedule and opioid type) and receptor expression compared to patients on long-term opioids for cancer pain [32,33,48-50]. Patients undergoing surgery are also exposed to a range of drugs during the operation which potentially impact on survival [32,33].

Two authors (JB and LZ) independently reviewed all titles and abstracts in order to assess their relevance for inclusion. Full text papers were retrieved for those fulfilling the criteria, and also for those publications for which the ability to assess their eligibility could not be assessed on the basis of the titles and abstracts alone. These authors then assessed the full texts of all potentially relevant studies. Disagreement at all stages was resolved by consensus and with recourse to a third review author (EB). The results of these searches are shown in the PRISMA Flow Diagram (Figure 2) [46].

Data extraction, assessment and analysis

JB and LZ independently extracted data regarding study design and results and assessed their quality. Data extracted included the type of study, study setting, study population (cancer type, stage, treatment) opioid used and dose, statistical analysis used and clinical outcome measures (e.g. survival). The methodological quality of each study was independently assessed by JB and LZ using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [51,52].

RESULTS

Studies included

We identified 526 unique records of which 20 studies were included in this systematic review (Figure 2 and Table 1). Due to the heterogeneous nature of these studies (in study design, duration/dose of opioid administered, measurement of survival) a meta-analysis was not possible and a narrative analysis has been performed. The studies were either in patients in the last days to weeks of life or in patients with months or years left to live. They were thus subdivided into studies assessing people in the last month of their life and those studies which were performed in patients with a longer prognosis (more than one month). The studies which assessed the effect of regular systemic opioid analgesia in patients at the end of life were generally low in quality using the GRADE system. This was principally due to their retrospective nature, and none were randomised controlled trials [53]. Studies assessing people with a longer prognosis tended to be of higher quality; these were mostly RCTs and prospective observation studies.

End of life studies:

Study characteristics

There were 13 studies which evaluated the effect of regular systemic opioid analgesia on survival in patients with cancer who were in the last days or weeks of life. Using the GRADE criteria, 11 of these were of a very low and 2 were of a low quality (Table 1). There were 11 retrospective studies and 2 represented a secondary data analysis (Table 1). The mean sample size was 254 patients. By their nature, these studies generally had a short follow-up, over days to a short number of weeks, sometimes just measuring opioid use in the last days of life. They were generally based in a

hospice/palliative care setting with a heterogeneous population with patients having a variety of cancer types. These studies tended to show that the opioid dose increased during hospice admission or with specialist palliative care input [54-57]. However, a large increase in the opioid dose did not generally occur in the last 2 days of life [54,55]. The time at which the opioid dose was reported was variable: including at baseline [17], measured daily [58], in the last 24h [53] or 48h [59] of life. The comparator varied between studies and included opioids vs no systemic opioids and high vs low dose opioids.

Effect of opioids on survival

The outcome of these studies differed. Some of the studies indicated a potential association of increased survival with higher doses of opioids or increases in opioid dose in the last days of life [53,55,60,61]. Others report no relationship between survival and overall dose or change in opioid dose [57-59,62,63]. In other studies, higher opioid dose or increasing doses of opioids were reported to be associated with a shorter survival (Table 1) [19,56,64].

From these studies, in mixed patient groups and settings, there is no clear association between opioid dose or increasing doses of opioids and survival; with some indicating that opioids might be associated with a decreased survival, and other studies suggesting that opioids improve survival, or have no effect. The appropriate use of higher opioid doses is emphasised [58] and many studies are based in a hospice, Hospital at Home Unit or in a specialist palliative care setting, which might have a skewed population as these patients probably represent a group of complex pain syndromes [19,53,61]. These studies can only look for an association between opioids and survival as there is no truly matched comparison to evaluate causality [53].

Long term studies:

Study characteristics

There are 7 studies which evaluated the effect of regular systemic opioid analgesia on survival in patients with cancer not undergoing surgery that lived for months to years. Using the GRADE criteria, 3 studies were moderate, 3 were low quality and 1 was very low quality (Table 1). There were 3 RCTs, 3 prospective studies and 1 retrospective study (Table 1). These studies tended to be multicentre (Table 1) [18,29,65,66]. The mean sample size was 485 patients. These studies included patients with diverse cancers as outlined in Table 1, but principally included patients with advanced cancers, with some studies having a relatively homogenous population [29,65,67]. The comparator varied between studies and included opioids vs no systemic opioids and high vs low dose opioids.

Effect of opioids on survival

All 3 RCTs, 2 of the 3 prospective studies and the retrospective study described a potential association between strong systemic opioid use or increasing dose and shorter survival. One RCT reported a non-significant trend for shorter survival in patients treated with oral opioids compared with intrathecal opioids for pain control (6 month survival 37% vs. 54%; $p=0.06$) [66]. Although the intrathecal group had a larger OME dose than the medically managed group, systemically the opioid concentration would be orders of magnitude less. Pain control was better and less opioid toxicity was reported in the intrathecal group which might have contributed to the potential survival benefit [66,68]. Another RCT evaluated opioid use on endocrine function and survival (survival was not the primary outcome), despite the median OME being low (females 40mg and males 80 mg/d), survival was shorter (median 78 days) in opioid-using male patients compared with non-opioid-users (median 132 days; $p=0.009$) [29]. Furthermore, in males opioid dose was highly correlated to low testosterone, and hypogonadal males had a shorter survival compared to those who were eugonadal [29]. In developing a prognostic model in chemotherapy for patients with advanced

prostate cancer, a secondary data analysis from 2 large chemotherapy RCTs showed that opioid use was independently associated with a shorter survival (Hazard Ratio [HR] 1.09) [65]. Importantly this study had a single time based assessment of yes/no opioid use without following the patients or looking at doses. In a conference abstract based on this data (n=836), there was a relationship between shorter survival and opioid at baseline and at 3 months, with a shorter survival if opioids were used both at baseline and at 3 months (median survival 18 months, compared with 27 months for patients not on opioids at baseline or 3 months; $p < 0.001$), although dose relationships were not explored [69].

In 2 of the 3 prospective studies, opioids were associated with a shorter survival [18,70]. Prescription of opioids stronger than tramadol was independently associated with a shorter survival (HR 2.5; $p = 0.001$), although only baseline opioid was reported with small numbers on opioids [18]. Strong opioids significantly decreased median survival in a haematological study (from a median survival of 191 days without opioids to 27 days with strong opioids; $p < 0.0001$) [70]. A longitudinal observational study showed no effect of opioids on survival up to 1 year, although the numbers were very small with only 21 people out of the cohort of 64 having died by 1 year, they also did not report the actual number of people in each group or how many had died [17]. In the retrospective study, increased opioid requirement after diagnosis was associated with a shorter progression free survival (HR 1.08; $p < 0.001$) and shorter overall survival (HR 1.07; $p < 0.001$), but was not associated with time to progression (as measured by prostate specific antigen), although this was associated with opioid requirement prior to diagnosis (HR 1.23; $p = 0.002$). Furthermore, for every 5mg/d increase in opioid requirement after diagnosis, the risk of death increased by 5% [67]. Finally, in this cohort, high levels of mu opioid receptors in the prostate cancer cells were associated with increased cancer progression and a shorter survival [67].

Several studies in different groups of patients with cancer have indicated that prolonged exposure to regular systemic opioid analgesia might be associated with a shorter survival; this seemed particularly evident with strong opioids (Table 1).

Limitations of the included studies

Many of the included studies had significant limitations; these are outlined in table 1 under the column confounders/limitations. These included limitations in the study design (mostly retrospective for end of life studies), as well as in the population, intervention, comparator and outcome measures.

Patient population: Some studies used discrete population with a very limited life expectancy such as hospice admission. Different baseline characteristics, such as those receiving higher doses of regular systemic opioid analgesia were more likely to be younger and male, there were also differences between types of cancer [19,55,60-63,66,70], with a minority of non-cancer patients included in some studies [19,57].

Intervention: The starting point for opioid use, the duration of opioid administration or when data was recorded differed between studies. Some studies only report the opioid dose at death or at baseline giving a cross-sectional view, not the overall accumulative opioid dose or how this changes. Morphine was the principal opioid in most studies and the different opioids used were pooled which although increased the number of participants in each group, removed the ability to explore any potential differences in effect on survival between opioids (however, it is useful to have an approximate equivalence between the different opioids as OME, which standardised opioid dose). There tended to be small numbers of patients on higher dose opioids [19,55,60,62,63]. In some studies, patients were only on opioids for pain [71], in other studies opioids were also used for different (or multiple) indications, such as sedation, dyspnea and cough [54,55,57,64]. In studies,

using a change of opioid dose, it is often unclear why the dose was changed; especially when it was decreased (e.g. was the patient sleepy or confused, and what the cause of this was) [58].

Comparison: In general the control groups were not directly matched, i.e. not patients who suffered from refractory severe symptoms but did not choose opioids. The comparison was not consistent between studies. This included patients who received an increase in opioids at the end of life with those who received no/little increase [54,61], or between patients on high doses of opioids vs lower doses [17] or no opioid [29,65,70]. The high dose opioid threshold varied between studies but was generally an OME dose above 120 - 300mg/d, although up to 600mg/d in one study [17,19,59,61]. Other studies used weak vs strong opioids [18,70]. Portenoy et al, reported that an OME above 60mg/d was equally associated with a shorter survival compared with below 51mg/d [19], this leads to the possibility that some other studies might miss an effect as they did not compare to a low enough dose. However, other studies showed the survival cut off to be at higher doses: Median survival 7d for OME<120 mg/d, 8d for OME 120–299 mg and 16d for OME>300 mg [53]. Many other drugs (including other analgesics and sedatives) were also used and often not precisely reported [53,57].

Outcome: The time point from which survival was measured varied, these included: from admission [54]; from maximum administered dose of opioids to death and dose escalation [19,61]; from last opioid dose change [19], or a designated time frame, such as 1 year [17]. In some studies survival was not a study end point or formed part of a secondary data analysis [19,63,65,66]. Some of these studies used multiple methods of measuring survival and generally only 1 analysis method showed association with survival [19,61]. Furthermore, not knowing what the patients' estimated prognosis was before starting on or having a dose escalation of opioid makes it hard to compare outcomes between groups.

DISCUSSION

This is the first systematic review to examine the association between regular systemic opioid analgesia and survival in all non-surgical patients with cancer. We found no clear relationship between opioid analgesia and survival in patients at the end of life, with days or weeks to live, this evidence comes from low quality studies, so should be interpreted with caution. However we found that in six out of the seven longer-term studies, opioid analgesia was (or had a tendency to be) associated with a shorter survival, although these studies did not have survival as a primary, appropriately powered, endpoint. In view of this we cannot make any definitive conclusions with regards to whether opioids affect survival in cancer patients. The data suggest that if opioids have an effect, this takes weeks to months to impact on survival (longer than the survival time of end-of-life patients), and therefore the chronic effects of opioids are more likely to be important than acute effects (Figure 1). Our findings are important because oncological therapy is improving and cancer patients are living longer. There is now a growing group of cancer survivors who often have long-term treatment-related effects such as pain which might be managed with long term opioids. However, there were a number of confounding factors and limitations in the design of many of the studies, all of which were of low to moderate quality.

Pain caused by cancer can be due to multiple mechanisms, involving numerous mediators (e.g. cytokines, nerve growth factor and endothelin-1) as well as peripheral and central neuro-immune interactions [72-74]. Cancer cells and activated immune cells can secrete endogenous opioids which interact with nociceptors [72,74]. Prescribed opioids produce pain relief principally by activating mu opioid receptors and by opening inwardly rectifying potassium channels; opioids also have downstream effects on intracellular messengers including the activation of phospholipase C, protein kinase C, mitogen-activated protein kinase and Nuclear Factor- κ B. [72,75-79].

Confounding factors

Survival is a multifactorial phenomenon influenced by complex factors, many of which might not be measurable [18,19,57]. The effect of opioids on survival is dependent on many other factors, including the effect of opioids on pain, and effect of pain on survival as well as the interaction between opioids, pain, wellbeing, emotional distress and depression [17]. Poor performance status, pain and strong opioids were associated with the a shorter survival [18], however in other studies those on higher dose opioids [63] or with escalated doses [61] had a better performance status. Higher pain scores in patients with cancer are associated with a shorter survival [17-20]. There is likely a triangulated relationship between opioids, pain and survival (as outlined in figure 1). It might be that in the studies where higher opioid doses are associated with a longer survival, that pain is better controlled and that these would have otherwise adversely impacted on survival [53,59-61]. Increasing pain from cancer, and thus higher opioid doses, could be related to more advanced disease which in itself will shorten survival [57,71]. At end of life, when the patient was unable to swallow, it is possible that analgesics only available orally were stopped, thus necessitating a higher dose of parenteral opioids to control pain. In some studies a lower opioid dose on admission increased survival, however this effect was lost following adjustment for other clinical factors, suggesting that the indication for the opioid may explain the survival differences [58].

Opioids other than morphine

Most of the studies have been done with morphine or pooling all opioids together irrespective of their differing effects [27], this leaves very little scope to determine if there is a difference between opioids, e.g. is it a group effect of all opioids or a morphine effect. Van Hooft and colleagues showed that taking opioids stronger than tramadol was an independent (taking pain into account) prognostic factor for short survival [18]. This might relate to patients being on weaker opioids having less

advanced disease. There was one study where controlled release oxycodone was assessed, the dose of this was not associated with survival at the end of life, although there was a trend for moderate oxycodone doses (OME 62-300 mg/d) to be associated with the longest survival and high doses (OME >300 mg/d) to be associated with the shortest survival [63].

Limitations of this review

The main limitation of this systematic review was that the results could not be pooled due to study heterogeneity. There were also methodological issues with many of the studies included, which were generally of a low quality. It is also possible that we have omitted relevant studies despite our detailed search strategy. In terms of the comparison of high vs. low opioids (or patients needing more of an increase in opioids) these are being used for symptom control and thus those patients needing more opioids might have worse symptoms or at least need a higher dose to control them. More advanced disease might mean increased levels of pain, necessitating higher doses of opioids. Furthermore in many studies the final symptom levels are not reported and it is unlikely all patients will have attained the same level of symptom control. There were marked inconsistencies between the patients included, the interventions, comparators and outcomes. Often there were many outcome measures or calculations used in the studies. Generally the opioids were converted to OME doses, it was unclear if they were they all converted in the same way between studies.

Future work

Future work needs to employ a robust methodology, either using large data sets or prospective cohorts to answer specific questions in a predefined way (although this will only show an association) or RCTs with survival as a primary endpoint to demonstrate causality. A placebo RCT design cannot be conducted in this situation as it is not ethical to withhold accepted, proven

analgesics which form the basis for pain guidelines globally. To randomise against another opioid would be possible, although this might not show a difference as we do not have the available data to know if this is potentially a class or individual opioid effect.

Conclusions

This systematic review has revealed that although there have been many studies assessing the effects of regular systemic opioid analgesia on survival, these tend to be of a low quality or survival is not the primary outcome. Despite the low quality and methodological difficulties, the end-of-life studies do not suggest a clear association of opioid use and survival. In view that they are low quality studies, this should be interpreted with caution. The longer term studies, which are generally of a higher quality, potentially indicate that regular systemic opioid analgesia is likely to be associated with a shorter survival, although these did not examine the effect of opioid on survival as a primary endpoint. In view of this, no definitive conclusions can be made with regard to whether opioids affect survival in cancer patients. Furthermore the differences between opioids have not been adequately explored to inform if opioid choice is relevant. Currently, based on available data, opioids should continue to be used for pain control in patients with cancer. An important limitation of research in this field is that the relationship between greater analgesic requirements and shorter survival may be mediated by painful progressive cancer.

Contributors

JB, LZ and EB contributed to study design, data collection and data analysis. KM performed the searches with JB. JB and EB drafted the article. JB provided the figures. MB contributed to study design and writing of the article. All authors were responsible for approval of the final report.

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Conflict of interest

All authors declare that there are no conflicts of interest.

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Figures

Figure 1: Potential mechanisms by which opioids might impact on survival in patients with cancer.

During acute administration high doses of some opioids might inhibit respiratory drive and shorter survival. Certain opioids have been shown to prolong the heart's QTc interval causing torsades de pointes. Chronic effects of opioids on cancer include apoptosis, angiogenesis and immunity. It is also possible that these immune effects might be offset as opioids decrease pain which itself might be immunosuppressive. Opioids might also have direct effects on the cancer cells. [16,21,28,67,80]

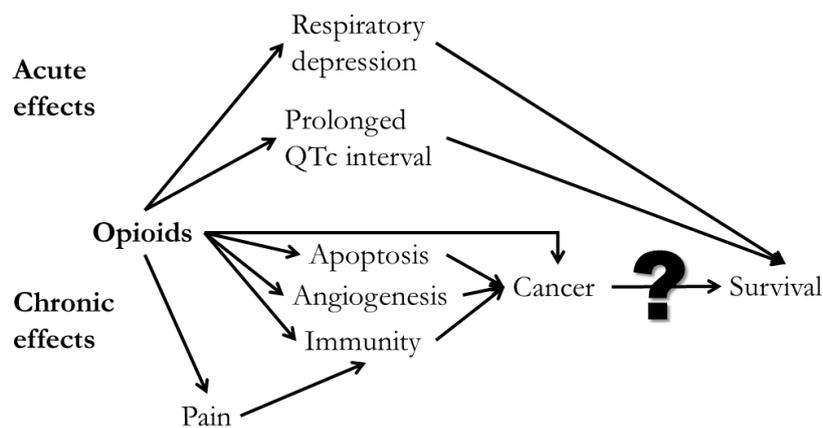


Figure 1

Figure 2: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009

flow diagram [46].

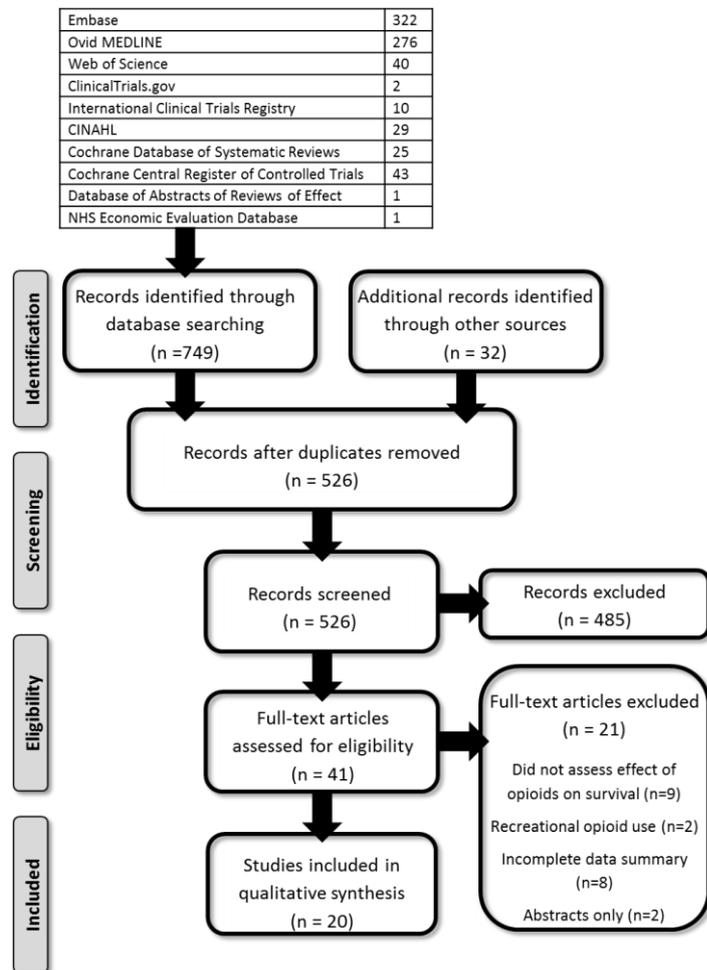


Figure 2

Table 1 – Effect of opioids on survival in patients with cancer.

Study	Research question / Aim	Study design	Patient population / setting	Intervention	Comparator	Outcome	Confounders/ limitations	Study quality (GRADE criteria)
End of life studies								
(Bercovitch, Waller et al. 1999) High dose morphine use in the hospice setting. A database survey of patient characteristics and effect on life expectancy [62].	What are the characteristics of patients requiring high dose morphine and the effect on survival?	Retrospective review	453 patients (from 651; 70%) on morphine with mixed cancers admitted to a hospice in Israel	High dose opioids (299-599 mg/d OME): 19 patients (4%). Very high dose opioids >599 mg/d OME: 36 patients (8%)	Low dose opioids (<299 mg/d OME): 398 patients (88%)	No statistical difference in survival time between opioid doses. Mean survival time: very high dose 13d; high dose 15d; low dose 14d	Retrospective Mixed cancers Opioids pooled Short term follow-up – from hospice admission. Small number of patients on high doses	Very Low
(Thorns and Sykes 2000) Opioid use in last week of life and implications for end-of-life decision-making [54].	Is symptom control with opioids associated with shortening of life in palliative care?	Retrospective review	Of 238 consecutive patients dying in a UK hospice, 212 (89%) received opioids in the last 24 h of life	Marked increase in opioid dose at the end of life 28 patients (12%)	No/small increase in opioid dose at the end of life 210 patients (88%)	No statistical difference in survival from hospice admission. Mean survival: 21d for dose increase group vs. 16d for no/small increase group (p=0.7)	Retrospective Mixed cancers Opioids pooled Small increase in the median daily opioid dose in the last week of life. Small numbers in dose increase group	Very Low
(Morita, Tsunoda et al. 2001) Effects of High Dose Opioids and Sedatives on Survival in Terminally Ill Cancer Patients [59].	Is opioid dose related to survival in last 2 days of life?	Secondary analysis of a prospective observational study	209 patients (172 on opioids) with mixed cancers on a palliative care unit in Japan	High dose opioids (>240mg OME/48h): 45 patients (22%)	No/Low dose opioids (<240mg OME/48h): 164 patients (78%)	No difference in survival time between opioid doses (p=0.23)	Mixed cancers Opioids pooled Short term follow-up. Small numbers of patients in higher dose opioid groups. Opioids only recorded in last 2 days of life	Low

(Bercovitch and Adunsky 2004) Patterns of high-dose morphine use in a home-care hospice service: should we be afraid of it? [60]	What are the characteristics of patients on high dose morphine use (>299mg/d) and does it affect survival?	Retrospective review	435 outpatients (from 661; 66%) on morphine with mixed cancers treated by a home-care hospice team in Israel	High dose opioids (>299 mg /d OME): 39 patients (9%)	Low dose opioids (5-299 mg /d OME): 396 patients (91%)	Higher opioid dose associated with longer median survival (P<0.001). Median survival: high dose 27d; low dose 18d; no opioids 22d	Retrospective Mixed cancers (analysed by cancer type). Only used opioid dose at baseline. Short term follow-up from Palliative care admission. Small number of patients on higher dose opioids. Younger patients in higher dose opioid groups	Very Low
(Good, Ravenscroft et al. 2005) Effects of opioids and sedatives on survival in an Australian inpatient palliative care population [53].	Does opioid and sedative medication use affect survival (from hospice admission to death) of patients in an Australian inpatient palliative care unit?	Retrospective review	229 patients (222 on opioids) admitted to a palliative care unit	High dose opioids (≥ 300 mg/d OME) in the last 24 h of life: 63 patients (28%)	No/low dose opioids (<300 mg/d OME) in the last 24 h of life: 166 patients (72%)	Survival from hospice admission to death was longer in patients on ≥ 300 mg/d OME (p=0.01). Mean survival: high dose 18d; low dose 12d	Retrospective Mixed cancers Opioids pooled Short term follow-up (from hospice admission to death), opioids recorded in the last 24h of life	Very Low
(Vitetta, Kenner et al. 2005) Sedation and analgesia-prescribing patterns in terminally ill patients at the end of life [57].	Does sedation hasten death in terminally ill patients?	Retrospective review	102 consecutive patients who died during admission to an Australian hospice. 92% cancer	Patients on opioids at admission (mean dose 111 mg/d OME): 56 patients (55%)	Opioids only prescribed during the last week of life (mean dose at last week 69 mg/d OME): 36 patients (35%)	Survival unrelated to opioid dose. Mean survival in patients taking opioids at admission: 26d. Mean survival if opioids only prescribed during the last week of life: 30d	Retrospective Mixed cancers and 8% non-cancer Opioids pooled Short term follow-up – from Palliative care admission (mean duration 26 days). No comparison to patients not on opioids	Very Low
(Bercovitch and Adunsky 2006)	To compare patients receiving	Retrospective review	97 consecutive patients with	High dose OxyContin (>150	Low dose OxyContin (0-30	Survival was not related to	Retrospective Mixed cancers	Very Low

High dose controlled release oxycodone in hospice care [63].	high dose OxyContin with patients taking lower doses		terminal cancer admitted to a hospice in Israel (taking oxycodone as the only opioid)	mg/d ~ >300mg/d OME): 18 patients (19%)	mg/d~ 0-60mg/d OME): 34 patients (35%) Moderate dose (31-150 mg/d ~ 62-300mg/d OME): 45 patients (46%)	OxyContin dose (p=0.12)	Survival not primary outcome Short term (mean survival 12 days)	
(Portenoy, Sibirceva et al. 2006) Opioid use and survival at the end of life: a survey of a hospice population [19].	Is survival after last opioid dose change associated with opioid dosing and other clinical characteristics?	Secondary analysis of prospective longitudinal survey data	725 patients with mixed cancer and non-cancer admitted to 13 hospices in the USA who had at ≥1 opioid dose change before death (from 1,306 patients) 42% cancer; 33% non-cancer; 25% both	Patients on >200 mg/d Intravenous morphine equivalent (IVME) (>600 mg/d OME): 85 patients (11.7%)	Patients on <200 mg/d IVME (<600 mg/d OME): 640 patients (88.3%) <17 mg/d IVME (<51 mg/d OME): n=61 (8.4%)	Shorter survival in patients on >20 mg/d IVME (>60 mg/d OME) (p= 0.0001). Mean survival: 27d for patients on <17 mg/d IVME vs. 12d for patients on 20-25 IVME. Opioid dose accounted for 6-8% of the overall effect on survival (depending on the analysis model)	Mixed diseases, not just cancer Opioids pooled Study not designed to assess opioids and survival. Small numbers of patients in lowest and highest dose opioid groups. Larger proportion of cancer patients in higher dose opioid groups. Younger patients in higher dose opioid groups	Low
(Bengoechea, Gutierrez et al. 2010) Opioid Use at the End of Life and Survival in a Hospital at Home Unit [61].	Do high doses of opioids, or increasing doses, influence survival in patients with terminal cancer who died in a Hospital at Home unit?	Retrospective cohort study	223 patients with mixed cancers admitted to the `Hospital at Home` unit in Spain	High dose opioids (OME≥120 mg): 99 patients (44%) (72% had previous opioids)	Low dose opioids (OME<120 mg): 124 patients (56%) (23% had previous opioids)	No difference in adjusted survival between groups (p=0.34). Longer survival in patients who received opioids ≥ twofold higher	Retrospective Mixed cancers Opioids pooled Short term follow-up – from `Hospital at Home` admission. Difference prior opioid exposure	Very Low

						than their initial doses during the last 7 days of life (22 vs. 9 days) (p<0.0001)		
(Radha Krishna, Poulouse et al. 2010) Opioid Use amongst Cancer Patients at the End of Life [55].	Do opioids in the last 48 hours of life influence survival in terminally ill cancer patients?	Retrospective review	238 cancer patients referred to a hospital-based specialist palliative care service in Singapore with terminal cancer and had died	On opioids: 192 patients (81%) 24 hours before death 187 patients (79%) on opioids, (median OME 57 mg/d). 48 hours before death 184 patients (77%) on opioids. (median OME 48 mg/d)	No opioids: 46 patients (19%)	No difference between opioid/no opioid groups at 24h before death (P=0.69). Longer survival (from referral to palliative care) in patients who were on high doses of opioids at 24h before death (P=0.004)	Retrospective Mixed cancers Opioids pooled Mixed indications for opioids Very small numbers of patients not on opioids or on higher dose/large increase opioid groups. Short term follow-up (median 5d) Opioid dose only recorded in last 48h of life	Very Low
(Da Costa Miranda, De Souza Fede et al. 2011) Doctor, how long? [64]	To quantify and identify variables influencing survival time in terminally sedated patients with cancer	Retrospective cohort study	181 consecutive patients with cancer who received terminal sedation in Brazil	Opioids as single drug for sedation: 87 patients (48%), with 128 (71%) needing a dose increase	Other sedatives, multiple sedatives, no dose increase in opioids: 94 patients (52%)	Opioids as single sedative drugs or an increase in dose were associated with shorter survival, odds ratio 1.44 (P=0.005)	Retrospective Mixed cancers No info on opioid dose or by how much increased. Very short term follow-up (median survival 27 h) Mixed indications for opioids, including as sedative	Very Low
(Lin, Lin et al. 2011) Symptom Patterns of Patients with Head and Neck Cancer in a Palliative Care	To describe the symptom patterns of patients with terminal head and neck cancer in the palliative care unit	Retrospective review	94 patients who died of primary head and neck cancer admitted to a palliative care unit in China	Opioid dose at death (median OME 160mg/d)	Opioid dose on admission (median OME 70mg/d)	Change in morphine dose correlated with survival time after hospice admission (p<0.001)	Retrospective Mixed cancers (although all head and neck) Opioids pooled Short follow-up (mean 22 days)	Very Low

Unit [56].								
(Azoulay, Jacobs et al. 2011) Opioids, Survival, and Advanced Cancer in the Hospice Setting [58].	Do opioids influence survival among advanced cancer patients following hospice admission?	Retrospective observational study	Data on 114 consecutive hospice in-patients (from 117) with advanced cancers in Israel	OME >120 mg/d on admission: 32 patients (28%) Last Day of Life: 39 patients (34%)	On admission: No opioids 29 patients (25%), 1–119 mg/d OME 53 patients (47%) Last Day of Life: No opioids 9 patients (8%) 1–119 mg/d- 66 patients (58%)	From hospice admission, opioid dose had no effect on survival after adjustment for confounding factors	Retrospective Mixed cancers Opioids pooled Short term follow-up – from Palliative care admission (mean 12 days)	Very Low

Studies in patients with a longer prognosis

(Smith, Staats et al. 2002) Randomized Clinical Trial of an Implantable Drug Delivery System Compared With Comprehensive Medical Management for Refractory Cancer Pain: Impact on Pain, Drug-Related Toxicity, and Survival [66].	What is the effect of intrathecal vs. oral opioids on pain control and toxicity at 4 weeks?	Multicentre randomised controlled trial	202 patients with mixed advanced cancers and refractory pain on at least 200mg OME in the USA (analysis on 148 patients)	Intrathecal opioids plus Comprehensive Medical Management: 73 patients (49%)	Oral opioids (Comprehensive Medical Management only): 75 patients (51%)	Intrathecal group had trend (p=0.06) for increased 6 month survival (54% vs. 37%)	Mixed cancers Opioids pooled Survival was monitored but was not a study endpoint	Moderate
(O'Mahony, Goulet et al. 2010) Psychosocial distress in patients treated for cancer pain: a prospective observational study [17].	Do opioids, depression, pain, wellbeing, desire for death, anxiety and PS impact on survival?	Longitudinal Observational Study	64 patients (52 had opioids) with mixed cancers in the USA	High dose morphine (>300mg/d) Number of people not reported	Low dose morphine (<300mg/d) Number of people not reported	No difference between groups on survival to 1 year	Mixed cancers Opioids pooled Small numbers (actual number of people in each group was not reported) Only used opioid dose at baseline. Multiple outcomes.	Very Low

							Effect of opioids on survival not primary outcome measure	
(van Hoof, Dijkgraaf et al. 2010) Independent predictors of survival in patients with incurable malignant gastric outlet obstruction: a multicenter prospective observational study [18].	Can baseline data in patients with incurable malignant gastric outlet obstruction (GOO) independently predict survival?	Multicentre prospective observational study	105 consecutive patients (Baseline data on 101) with malignant GOO treated with duodenal stent, in the Netherlands	Opioids stronger than tramadol 19 patients (19%) at Baseline	No opioids/ opioids not stronger than tramadol 82 patients (82%) at Baseline	Opioids stronger than tramadol were associated with a shorter survival (Hazard Ratio 2.5) (p=0.001)	Mixed cancers Opioids pooled Only subdivided opioids into tramadol vs. stronger opioids small numbers of patients on strong opioids Only baseline opioid use reported	Low
(Skipworth, Moses et al. 2011) Interaction of gonadal status with systemic inflammation and opioid use in determining nutritional status and prognosis in advanced pancreatic cancer [29].	Investigation into the interaction of gonadal status with systemic inflammation and opioids in determining nutritional status and prognosis in advanced pancreatic cancer	A multicentre randomised trial	167 patients (from 175 randomised) with advanced pancreatic cancer; 43 on opioids, in the USA	Patients on opioids: Median OME dose females 40mg males 80 mg 25 male (15%) 18 female (11%)	Patients not on opioids: 65 male (39%) 59 female (35%)	Survival was shorter in male patients using opioid compared with non-opioid-users; median 78d vs 132d (p=0.009)	Opioids pooled Small numbers of patients when subdivided into sex	Moderate
(Zylla, Gourley et al. 2013) Opioid Requirement, Opioid Receptor Expression, and Clinical Outcomes in Patients With Advanced Prostate Cancer [67].	What is the association of opioid dose on cancer progression and survival in patients with metastatic prostate cancer?	Retrospective Observation Cohort analysis	593 patients with stage IV prostate cancer In the USA (test cohort - 113 from Minneapolis VA Tumour Registry; validation cohort - 480 patients from VA Central Cancer Registry)	Average opioid dose (OME) for 1 year before diagnosis and from diagnosis to death/last follow up	Compared to other opioid doses	Increased opioid requirement was associated with shorter survival (p<0.001)	Retrospective Opioids pooled	Low

(Halabi, Lin et al. 2014) Updated Prognostic Model for Predicting Overall Survival in First-Line Chemotherapy for Patients With Metastatic Castration-Resistant Prostate Cancer [65].	To develop a Model for Predicting Survival in Chemotherapy for Patients With Metastatic Castration-Resistant Prostate Cancer	Data from 2 phase III RCTs (1050+942 patients)	1992 patients with metastatic castration-resistant prostate cancer - data were split into training, testing and validation sets	Patients on opioids: 521 patients (29%)	Patients not on opioids: 1249 patients (71%)	Opioid use was associated with a shorter survival (Hazard Ratio 1.09)	Secondary data analysis. Data for a specific patient group did not check dose effect	Moderate
(Kripp, Willer et al. 2014) Patients with malignant hematological disorders treated on a palliative care unit: prognostic impact of clinical factors [70].	What are the potential prognostic clinical and laboratory factors in patients with haematological diseases admitted to a palliative care unit?	Analysis of prospectively collected data from an observation Cohort	290 consecutive patients (230; 79% on opioids) with mixed haematological diseases admitted to a palliative care unit in Germany (from 466 consecutive admissions)	Patients on strong opioids: 165 patients (72%)	Patients not on strong opioids: 125 patients (28%)	Strong opioids associated with shorter survival; median 27d vs 191d (p<0.0001)	Single site, Haematological malignancies at different stages (small numbers for some diseases), opioids pooled - did not check dose effect. Patients admitted at different disease stages	Low

Abbreviations: OME - Oral Morphine Equivalents; IVME - Intravenous morphine equivalent; WHO – world health organisation; PS - performance status; VA - Veterans Affairs;